DETAILED ACTION

Application Status

1. In response to the previous Office action, a non-Final rejection (mailed on 04/03/2008), Applicants filed a response and amendment received on 10/01/2008. Said amendment amended Claims 1, 5, 10-11, 13, 24, 32, 40, 47 and 49-50.

Claims 1-52 are pending in the instant application. Claims 1-12 and 16-52 are withdrawn from consideration as non-elected inventions as noted in the previous office action.

Claims 13-15 will be examined herein.

Priority

2. It is noted that applicant has updated the status of the priority in the 1st paragraph by virtue of specification amendment filed on 10/01/2008 as suggested by the Examiner in the previous office action.

Withdrawn-Non-Compliance with Sequence Rules

3. The previous objection for non-compliance with the sequence rules because the Figure 1a teaches three amino acid sequences without appropriate SEQ ID NOs is withdrawn by virtue of applicant's amendment (see bottom of page 2 of specification amendment filed on 10/1/2008).

4. The previous objection for non-compliance with the sequence rules because Figure 8a teaches five amino acid sequences without appropriate SEQ ID NOs is withdrawn by virtue of applicant's amendment (see bottom of page 3 of specification amendment filed on 10/1/2008).

5. The previous objection for non-compliance with the sequence rules because Figure 43 teaches five amino acid sequences without appropriate SEQ ID NOs is withdrawn by virtue of applicant's amendment (see bottom of page 4 to top of page 5 of specification amendment filed on 10/1/2008).

Compliance with Sequence Rules

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to fully comply with the requirements of 37 C.F.R. 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

(a) The sequence represented by "CONSENSUS" in Fig. 8B represents an amino acid sequence without a sequence identifier, *i.e.*, "SEQ ID NO:". Labeling using a SEQ ID NO: must be inserted into the brief description of the drawings or into the Figure directly.

(b) The sequence of "NEP-motif-1" and "NEP-motif-2" in Figure 43 represents an amino acid sequence without appropriate SEQ ID NOs. Labeling using a SEQ ID NO: must be inserted into the brief description of the drawings or into the Figure directly.

If the noted sequences are in the sequence listing as filed, Applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. If the noted sequences are not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

Withdrawn-Objections to the Specification

7. The previous objection to the specification for reciting "MPEP" on page 23, line 26 which should be "MEPE" is withdrawn by virtue of applicant's amendment (see middle of page 5 of specification amendment filed on 10/1/2008).

Maintained-Claim Objections

8. The previous objection of Claims 13-15 because of the use of an abbreviation in Claim 13 (Claims 14-15 dependent therefrom), which should be spelled out on a first

appearance in claims (i.e., the acidic-serine-aspartate-rich-MEPE as in page 6, bottom), is maintained.

Applicant argues that adding "acidic-serine-rich-MEPE" in claim 13 overcomes the instant objection. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. As noted previously, it should be --- acidic-serine-aspartate-rich-MEPE---. See, *e.g.,* specification at p. 6, lines 22-23.

New and Maintained-Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 13-15 are rejected under 35 U.S.C. 112, first paragraph, new matter, as failing to comply with the written description requirement. The claim(s) contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. As noted above, this is a new matter rejection.

The instant rejection is necessitated by the instant claim amendment.

Claim 13 (Claims 14-15 dependent therefrom) recites "acidic-serine-rich-MEPE", where the original application fails to provide adequate descriptive support for this limitation. To the extent the recitation of "acidic-serine-rich-MEPE" represents a distinct genus of peptides from "acidic-serine-aspartate-rich-MEPE" peptides, the added

limitation is considered to be new matter. The applicant is advised to point out the support in the original disclosure or amend the instant claims. As noted above in the claim objection, amending the recitation to --- acidic-serine-aspartate-rich-MEPE--- is recommended by the Examiner to overcome the instant rejection.

10. The previous rejection of Claims 13-15 are rejected under 35 U.S.C. § 112, first paragraph, **written description**, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention; is maintained for the reasons below. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicant points out that Figure 1a depicts the acidic-serine-aspartate-rich-MEPE (ASARM) peptide motif for human, mouse, and rat species. Applicant argues that, as depicted in Figure 1a, the carboxy terminal residues of ASARM are highly conserved from species to species; and the release of this fragment from any of these species would provide a peptide motif that is resistant to proteases, providing a method for controlling ectopic mineralization (see bottom of page 14, Remarks filed on 10/1/2008). Applicant also describes the structural features of ASARM on page 15, lines 1-7, Remarks filed on 10/1/2008, and argue that the unique combination of amino acids is only found in "ASARM peptide or variant thereof" for the support of the written description requirement.

Applicant's argument is not found persuasive. Contrary to applicants' argument, there is no claim limitation that requires the genus of ASARM peptides to maintain a common structural feature. Here, the instant claims are not limited to a method of administering an ASARM having the structural feature described on top of page 15 lines 1-7, Remarks filed on 10/1/2008; but encompasses any ASARM peptide fragment or variant thereof (which includes any substitution, addition, deletion and/or combination thereof) as defined in the specification at, *e.g.,* page 24, lines 9-10. As noted previously, the Examiner acknowledges that applicants have described ten representative species of the genus of recited ASARM peptides (i.e., SEQ ID NO: 1-5, 8, 9, 13-14 and 16; see page 7, lines 5-6, non-final office action mailed on 4/3/2008). However, these species in combination with the remaining disclosure of the specification and prior art fails to teach a sufficient correlation between the structure of an "ASARM peptide" as encompassed by the claims and the function of inhibiting ectopic tissue mineralization; thus, the recited genus of ASARM peptides is not adequately described by the instant specification.

Applicant has stated that "VandenBos does not describe the ASARM peptide sequence", and at the same time, "Applicant clearly points out the presence of this motif in osteopontin" of the VandenBos reference (see page 15, lines 13-15, Remarks filed on 10/01/2008); and the applicant further argues VandenBos taken together with instant Figure 1a demonstrate that "ASARM peptide or variant thereof" would be expected to affect ectopic tissue mineralization.

However, it is unclear how applicants make conflicting statement as emphasized by the underlining above and use it as supporting description of the recited genus of ASARM peptides of the claimed invention. For the record, the description of one species of the genus of ASARM peptides (which is used in claimed method) in the osteopontin of VandenBos is clear in view of applicants' acknowledgement in the Remarks filed on 10/1/2008 as well as by virtue of a clear indication and labeling by "ASARM-PEPTIDE" in the instant Figure 1B. However, the teachings of three species of ASARM peptides in instant Figure 1 and one species taught by VandenBos do not provide sufficient correlation between the structure of genus ASARM used in claimed method and the function of ectopic tissue mineralization inhibition; wherein the genus of ASARM peptide encompasses any fragment or any variant thereof as noted above and as noted in the previous office action.

Thus, given broad and reasonable interpretation in light of the instant specification, the "ASARM peptide" encompasses a very broad genus of peptides as described in the breadth of claims in the previous office action (see the previous office action mailed out on 4/3/2008, bottom of page 6 to top of page 7) including osteopontin as well as any ASARM peptide fragment or variant thereof without sufficient correlation between structure of any ASARM peptide and the function thereof (i.e., inhibiting ectopic tissue mineralization); and one skilled in the art would not be in possession of the claimed genus method by the instant specification.

11. The previous rejection of Claims 13-15 under 35 U.S.C. 112, first paragraph,

scope of enablement, because the specification, while being enabling for a method for treating or inhibiting ectopic tissue mineralization in a subject comprising administering to the subject the ASARM peptide of SEQ ID NO: 1, 2, 3, 4, 5, 8, 9, 13, 14, or 16, does not reasonably provide enablement for a method comprising administering any "ASARM peptide" as broadly encompassed by the claims for treating or inhibiting ectopic tissue mineralization in a subject; is maintained for the reasons below.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicants argue the instant rejection should be withdrawn because the figures, examples, and specification point out the unique combination of amino acids, inter alia, serine, glutamic and aspartic acids, that comprise ASARM peptide and how these amino acids are highly conserved from species to species (Figure 1a and from peptide to peptide (Figure 1b); see bottom of page 15, Remarks filed on 10/1/2008.

The Examiner acknowledges that the Figure 1 discloses the species of ASARM peptide (i.e., SEQ ID NO: 1-3) used in the claimed invention as noted in the previous office action. However, the claimed method encompasses the use of a very broad scope of ASARM peptides since the "ASARM peptide disclosed herein can also comprise any ASARM peptide fragment or variant thereof" (see page 24, lines 9-10), which encompasses a method of administering any ASARM fragment and variant thereof from the polypeptide (e.g., SEQ ID NO: 1-5, 8, 9, 13-14 and 16 with any deletion, addition, substitution and/or combination thereof) given broad and reasonable interpretation of "fragment" or "variant" of ASARM peptide without any direction or

guidance on how to make and use any other ASARM peptide for the method of administering for treating or inhibiting ectopic tissue mineralization in a subject. Applicants also acknowledges that the intact protein DMP-1 having an ASARM-motif acts as a nucleator of mineralization (see bottom of page 16, Remarks filed on 10/1/2008) wherein the prior art and the instant application do not teach when a polypeptide having ASARM-motif is acting as an inhibitor or a nucleator of mineralization. Therefore, it is unpredictable as to which ASARM peptides encompassing any fragment and any variants of, *e.g.,* SEQ ID NO: 1-5, 8, 9, 13-14 and 16, can to be administered as set forth in the method of Claims 13-15 by one skilled in the art such that the claimed method of administering the full scope of ASARM peptides would reasonably be expected to *inhibit* mineralization. The said unpredictability makes the relative skill required in the art very high. For all of the above reasons, it would require undue experimentation for a method of administering the full scope of recited ASARM peptides such that ectopic tissue mineralization is inhibited.

Maintained-Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. The previous rejection of Claims 13-15 under 35 U.S.C. 102(b) as being anticipated by VandenBos et al. (1999, J Dent Res, Vol. 78, page 1688-1695) as

evidenced by McKee et al. (1996, Microsc Res Tech, Vol. 33, pages 141-164) is maintained for the reasons of record and the reasons set forth below.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicant argues that "VandenBos et al. do not teach that osteopontin inhibits mineralization" (see page 16, line 16, Remarks filed on 10/01/2008) supported by the VandenBos et al. teaching that OPN immunostaining was restricted to the mineralized area (see page 16, lines 26-27, Remarks filed on 10/01/2008). Applicant argues that VandenBos does not teach that osteopontin is a mineralization inhibitor because VandenBos clearly teaches (on page 1690, column, 2, line 7 of the paragraph titled "Mineralizing collagen sheets") that as the carrier material mineralized, a progressive influx of ^{125}I-OPN was observed; and argue that the same section at paragraph 3, VandenBos teaches "while all control implants proved to be OPN-negative, alkalie-phosphatase-complexed implants stained positive with the OPN antibody and the immunostaining was restricted to the mineralized area (emphasis added). Applicant argues that the presence of an ASARM-like motif in osteopontin, DMP1 does not indicate that these larger protein molecules inhibit mineralization, instead, the reverse is the case and in an intact protein such as DMP-1, the ASARM-motif acts as a nucleator of mineralization and serves to epistatically orient hydroxyapatite during formation. Thus, applicant argues that the Examiner misconstrued the disclosure of VandenBos et al.; and instant rejection should be withdrawn.

As noted in the previous office action, VandenBos et al. teach the step of administering osteopontin. Contrary to the applicant's argument, the inhibition of mineralization is the result of the administration of osteopontin as evidenced by McKee et al. (emphasis added; see the previous non-final office action mailed out on 4/3/2008; page 10, line 19 on page 10 - page 11, line 2 on page 11); wherein McKee et al. clearly state that "... osteopontin (OPN) all are consistent with the notions of this protein functioning as an inhibitor of mineralization...", (emphasis added; see the Abstract). As applicants acknowledged, the osteopontin by VandenBos et al. "is associated with mineralizing" wherein the association of osteopontin in an ectopic tissue (i.e., abnormal, as noted in 2nd line, page 11) is normal since the inhibition of mineralization in tissue has to occur in the process (or at the site of) mineralization. Contrary to the applicant's argument the instant application is silent about the function of osteopontin and the Examiner requests that applicants point out the teaching about osteopontin in the instant application and why it is not encompassed by the instant ASARM peptide when applicants acknowledge clearly that osteopontin has ASARM-peptide in the argument on page 15, lines 14-15 (see Remarks filed on 10/1/2009). As noted above and in the previous office action, the osteopontin by VandenBos is encompassed by the "ASARM peptide" because it contains the ASARM-motif by the instant specification's disclosure of "ASARM-motif is found in members of the SIBLNG protein family (MEPE, DMP-1, osteopontin, DSPP)" (see page 7, line 5), as described by the instant Figure IB" (see the non-final office action mailed out on 4/3/2008, page 11, lines 3-7) and as evidenced by McKee, has mineralization inhibiting activity.

The Examiner is unclear how and why the additional teachings about the status of mineralization process presented by VandenBos et al., support the applicant's argument (i.e., the VandenBos et al. do not teach claimed invention). The fact that immunostaining restricted to the mineralized area when the alkaline phosphatase is complexed in implants **does not** teach that the **osteopontin is not involved in the inhibition of mineralization**. However, as noted earlier, the fact that the inhibition of mineralization by osteopontin is clearly supported and evidenced by the objective statements by McKee et al. (i.e., "... osteopontin (OPN) all are consistent with the notions of this protein functioning as an inhibitor of mineralization...", emphasis added; see the Abstract) wherein the osteopontin is encompassed by the instant "ASARM-peptide" used in claimed method as noted above.

While applicant asserts intact DMP-1 polypeptide having an ASARM-motif acts as a nucleator of mineralization (see bottom of page 16, Remarks filed on 10/1/2008), the instant rejection is based on the administration of osteopontin as taught by VandenBos et al., *not* administration of intact protein DMP-1 having an ASARM-motif.

Thus, the osteopontin administered by VandenBos et al. during the injection meets the instant limitation of administering ASARM peptide such that ectopic tissue mineralization is inhibited as evidenced by McKee.

As noted in the previous office action mailed out on 4/3/2008 (see bottom of page 11), According to MPEP §2111.02, II, "During examination, statements in the preamble reciting the purpose or intended use of the claimed invention must be evaluated to determine whether the recited purpose or intended use results in a structural difference

(or, in the case of process claims, manipulative difference) between the claimed invention and the prior art. It is noted that the recitation of "treating or inhibiting ectopic tissue mineralization in the subject" before the term "comprising" in Claim 13 is a preamble reciting intended use and do not contribute to a manipulative difference in recited steps of administering ASARM peptide. Claim 13 also recites "thereby treating or inhibiting ectopic tissue mineralization in the subject" at the end, which is interpreted as simply expressing the intended result of the process step and do not contribute to a positive manipulative step in the method claim. Thus, the method of VandenBos et al. meets the limitations of Claim 13. Claim 14 limits the subject to having "ectopic mineralization associated with periodontal disease" and claim 15 limits the subject to having "ectopic mineralization associated with kidney disease". However, these claims have been interpreted as only requiring that the subject have ectopic mineralization and not periodontal disease or kidney disease, since neither of these claims actually requires the subject to have periodontal disease or kidney disease. Moreover, the applicants acknowledges that "the teaching of VandenBos taken together with Applicant's disclosure in figure 1a ... "ASARM peptide or variant thereof" as recited in Claims 13 would be expected to affect ectopic tissue mineralization" (see page 15, lines 15-20, Remarks filed on 10/1/2008). Thus, a method of VandenBos et al. also meets limitations of Claims 14 and 15.

Conclusion

13. Claims 13-15 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered section in this Office action to be fully responsive in prosecution.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALEXANDER D. KIM whose telephone number is (571)272-5266. The examiner can normally be reached on 10AM-6:30PM.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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